

TREATMENT OF HOOKWORM DISEASE WITH A COMBI-  
NATION OF CARBON TETRACHLORIDE AND OIL  
OF CHENOPODIUM. COMPARISON OF RESULTS  
OF SIMULTANEOUS AND DELAYED ADMINIS-  
TRATION OF MAGNESIUM SULPHATE.\*

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Since the first report of Hall (1) on the efficacy of carbon tetrachloride in the treatment of hookworm disease, the drug has been extensively used in a variety of dosages and combinations. As with all other anthelmintics effective against uncinaria, its introduction on a large scale in field operations has been followed by cases of fatal intoxication. Smillie and Pessoa (2) suggested the combination of ascaridol, the active principle of oil of chenopodium, with carbon tetrachloride, since experimental work showed that neither drug increased the toxicity of the other, while their specific actions when given in small combined doses seemed to be complementary. Carbon tetrachloride was found to be more effective against female hookworms and ascaridol more effective against male hookworms and ascarides. The dosage recommended was 2 c.c. of a three to one mixture of carbon tetrachloride and ascaridol. Lambert (3) has recently treated two thousand cases with a combination of four parts of carbon tetrachloride and one part of ascaridol and claims this is the best anthelmintic yet found for a mixed infection with hookworms and ascaris.

Hall (4) following the work of Macht and Finesilver (5) who showed that "the simultaneous administration of magnesium sulphate will diminish the absorption of the drug and thereby increase the safety and lessen the symptoms," has recently published the results of experiments indicating that the simultaneous administration of magnesium sulphate does not diminish the efficacy of carbon tetrachloride in the expulsion of hookworms in dogs. Lambert (3), (6) has used magnesium sulphate simultaneously with carbon tetrachloride and with combi-

\* This report is based on work carried out as part of the campaign against Hookworm Disease in Paraguay and is being conducted with the financial cooperation of The International Health Board and the Republic of Paraguay.

nations of this drug with ascaridol and gets "fewer symptoms following their administration and equal efficiency by worm count test."

Leach, et al., (7) using large doses of carbon tetrachloride found lightly infected cases difficult to clear.

Darling, (8) using various drugs, but more especially chenopodium in 1.5 c.c. doses, observed that the percentage of worms removed in each case was greater for the first treatment, when the number of worms harboured was large, than for the second treatment, when the number of worms harboured was small. Darling refuses to accept the explanation that this difference in percentage removed is due to the persistence of the more resistant forms, and gives data on light and heavily infested cases to show that the same difference is noted in previously untreated lightly and heavily infested cases.

The work on which this report is based, was planned to determine:

1. The degree of infestation and species of hookworms harbored by Paraguayan soldiers.
2. The efficiency against hookworms of the routine treatment with a combination of three parts of carbon tetrachloride and one part of oil of chenopodium, used in adult dosage of 2.4 c.c., correlated in regard to species and sex, as well as to lightly and heavily infested cases.
3. The effect of simultaneous administration of a saturated solution of magnesium sulphate, as compared with the effect of the same purgative administered two hours after treatment.

#### METHOD.

A group of forty soldiers, in the age group 17 to 24 years, with previous military service \* of from 3 to 30 months, was divided into two groups of twenty each.† Both groupings were given 2.4 c.c. of a combination of three parts of carbon tetrachloride ‡ and one part of oil of chenopodium, i.e. 1.8 c.c. of the former and .6 c.c. of the latter. Group 1, Cases 1 to 20, received 40 grams of magnesium sulphate in saturated solution two hours after treatment. Group 2, Cases 21 to 40, received the same purgative simultaneously with the combination of carbon tetrachloride and chenopodium. Treatments were actually

\* Military service in Paraguay probably does not tend to diminish the degree of hookworm infestation, as the soldiers are generally unshod.

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‡ The carbon tetrachloride administered was purchased from the Eastman Kodak Company, Rochester, New York, in November 1923.

carried out in groups of ten because of inadequate hospital facilities. All cases were hospitalized for sixty hours.

Careful discipline was maintained and all stools preserved in numbered 'jerries' for forty-eight hours after treatment. Worm counts were made, classifying all hookworms as to the day passed, species, and sex.

Fifteen days after the trial treatment, the men were brought into the hospital a second time and given the standard (9) test treatment of 3 c.c. of oil of chenopodium, in three divided doses of 1 c.c., at hourly intervals, followed in one and a half hours by magnesium sulphate. The test treatment was preceded by a purgative dose of magnesium sulphate on the eve of treatment. Stools were again preserved for forty-eight hours, and the hookworms counted and classified as to species and sex.

The patients were given a purgative of magnesium sulphate on the day following each treatment to insure second day evacuations.

#### RESULTS OF EXPERIMENT.

Table I gives in detail by species, sex and day expelled, the hookworms encountered in the twenty soldiers of Group 1, together with the residual worms encountered in the test treatment with 3 c.c. of chenopodium. Table II gives the same data for Group 2. Table III gives a comparison of the totals of Tables I and II and the total results for the entire forty soldiers treated.

Tables IV, V, VI, and VII were compiled from the data presented in Tables I, II, and III.

It would be difficult to secure more closely identical results from two experimental groups than those presented by Tables I, II, and III. Group 1 had 10,618 hookworms, of which 10,267 were expelled by the trial treatment: Group 2 had 10,601 hookworms, 10,211 of which were expelled by the trial treatment.

Table IV shows, however, that the time of expulsion varies in the two groups. Group 1, which received its magnesium sulphate two hours after treatment, expelled 86.3 per cent. of trial treatment worms in the first twenty-four hours. Group 2, which received its magnesium sulphate simultaneously with the anthelmintic mixture expelled only 57.1 per cent. of its trial treatment worms in the first 24 hours. That this variation was due to delayed expulsion and not delayed killing, is indicated by the large number of partly digested worms encountered in second day stools of Group 2.

TABLE I.

Case num- ber.	First treatment.—1.8 c.c. CCl <sub>4</sub> + .6 c.c. chenopodium. Magnesium sulphate 2 hours later.													Test treatment.—3 c.c. chenopodium.							Total hook- worms.
	First 24 hours.				24 to 48 hours.				Totals 48 hours.				Total necators and ancy- lostomes.	First 48 hours.				Total necators and ancy- lostomes.			
	Necator.		Ancylos- tome.		Necator.		Ancylos- tome.		Necator		Ancylos- tome.			Necator.		Ancylos- tome.					
	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.		F.	M.	F.	M.				
1....	253	299	36	33	0	0	0	0	253	299	36	33	621	0	2	2	1	5	626		
2....	139	181	19	5	6	17	1	2	145	198	20	7	370	0	8	8	7	23	393		
3....	92	99	8	8	7	37	2	4	99	136	10	12	257	0	1	0	1	2	259		
4....	135	134	30	24	7	24	7	10	142	158	37	34	371	0	0	0	0	0	371		
5....	326	377	19	16	13	41	4	5	339	418	23	21	801	0	1	10	1	12	813		
6....	370	303	33	32	3	38	0	0	373	341	33	32	779	6	1	8	1	16	795		
7....	66	44	1	0	2	7	0	0	68	51	1	0	140	0	0	1	1	2	122		
8....	554	597	35	25	13	24	0	2	567	621	35	27	1,250	8	2	12	2	24	1,274		
9....	161	164	12	13	16	33	5	6	177	197	17	19	410	0	0	1	1	2	412		
10....	104	103	5	5	65	125	7	1	169	228	12	6	415	1	6	0	0	7	422		
11....	472	496	34	18	6	16	5	9	478	512	39	27	1,056	0	0	10	2	12	1,068		
12....	126	125	24	28	12	37	3	5	138	162	27	33	360	0	0	20	13	33	393		
13....	266	285	28	9	56	121	20	12	322	406	48	21	797	1	1	26	17	45	842		
14....	21	14	8	6	4	15	4	2	25	29	12	8	74	3	6	15	5	29	103		
15....	42	41	8	3	95	116	2	2	137	157	10	5	309	10	16	10	8	44	353		
16....	175	274	15	6	13	77	4	2	188	351	19	8	566	0	2	7	2	11	577		
17....	15	17	0	0	3	0	0	0	18	17	0	0	35	0	0	0	0	0	35		
18....	140	178	17	18	2	2	0	0	142	180	17	18	357	1	0	2	2	5	362		
19....	401	623	13	12	52	78	0	0	453	701	13	12	1,179	3	46	9	6	64	1,243		
20....	20	17	3	2	31	64	0	3	51	81	3	5	140	0	1	12	2	15	155		
Total.	3,878	4,371	348	263	406	872	64	65	4,284	5,243	412	328	10,267	33	93	153	72	351	10,618		

F. = Female. M. = Male.

TABLE II.

Case num- ber.	First treatment.—1.8 c.c. CCl <sub>4</sub> + .6 c.c. chenopodium. Magnesium sulphate at same hour.													Test treatment.— 3 c.c. chenopodium. 48-hour count.						Total hook- worms.
	First 24 hours.				24 to 48 hours.				Totals 48 hours.				Total necators and ancylos- tomes.	Necator.		Ancylos- tome.		Total necators and ancylo- stomes.		
	Necator.		Ancylos- tome.		Necator.		Ancylos- tome.		Necator.		Ancylos- tome.			Necator.		Ancylos- tome.				
	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.		F.	M.	F.	M.			
21....	141	126	23	7	24	56	0	2	165	182	23	9	379	1	0	1	0	2	381	
22....	7	16	4	1	622	539	28	10	629	555	32	11	1,227	14	60	7	13	94	1,321	
23....	53	52	3	5	13	16	0	5	66	68	3	10	147	0	4	0	0	4	151	
24....	250	202	22	17	57	67	9	6	307	269	31	23	630	2	7	17	3	29	659	
25....	202	174	3	2	152	183	9	9	354	357	12	11	734	1	16	2	1	20	754	
26....	403	455	23	14	14	39	8	7	417	494	32	21	964	0	1	24	10	35	999	
27....	382	324	23	23	178	212	10	11	560	536	33	34	1,163	0	0	1	2	3	1,166	
28....	337	273	31	21	76	86	8	16	413	359	39	37	848	0	0	10	6	16	864	
29....	74	78	18	13	8	23	3	2	82	101	21	15	219	0	0	6	1	7	226	
30....	145	183	0	0	12	24	1	5	157	207	1	5	370	0	0	0	0	0	370	
31....	44	28	2	3	87	95	10	12	131	123	12	15	281	2	20	10	3	35	316	
32....	54	34	4	3	44	69	7	5	98	103	11	8	220	0	0	4	3	7	227	
33....	5	2	2	1	2	2	0	0	7	4	2	1	14	0	0	0	0	0	14	
34....	76	79	10	4	68	101	9	5	144	180	19	9	352	1	13	9	8	31	383	
35....	79	81	7	4	107	217	9	10	186	298	16	14	514	0	0	24	12	36	550	
36....	87	76	25	4	234	232	27	12	321	308	52	16	697	0	1	7	4	12	709	
37....	248	286	15	4	22	16	0	4	270	302	15	8	595	4	5	1	0	10	605	
38....	13	4	1	2	48	59	3	13	61	63	4	15	143	0	2	9	10	21	164	
39....	3	5	0	0	58	60	11	3	61	65	11	3	140	0	0	1	2	3	143	
40....	186	192	19	8	58	108	2	1	244	300	21	9	574	1	2	20	2	25	599	
Total.	2,789	2,670	236	136	1,884	2,204	154	138	4,673	4,874	390	274	10,211	26	131	153	80	390	10,601	

F. = Female. M. = Male.

TABLE III.  
Summary of groups 1 and 2.

Cases.	Trial treatment.—1.8 c.c. CCl <sub>4</sub> + .6 c.c. chenopodium.													Test treatment.— 3 c.c. chenopodium. 48 hours.					Total hook- worms.
	First 24 hours.				24 to 48 hours.				Totals 48 hours.				Total necators and ancylos- tomes.	Necator.		Ancylos- tome.		Total necators and ancylo- stomes.	
	Necator.		Ancylos- tome.		Necator.		Ancylos- tome.		Necator.		Ancylos- tome.			Necator.		Ancylos- tome.			
	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.		F.	M.	F.	M.		
1-20 Group 1	3,878	4,371	348	263	406	872	64	65	4,284	5,243	412	328	10,267	33	93	153	72	351	10,618
21-40 Group 2	2,789	2,670	236	136	1,884	2,204	154	138	4,673	4,874	390	274	10,211	26	131	153	80	390	10,601
1-40 Total	6,667	7,041	584	399	2,290	3,076	218	203	8,957	10,117	802	602	20,478	59	224	306	152	741	21,219

F. = Female. M. = Male.

TABLE IV.

	Total cases 1-40, trial and test treatments.		Group 1. Cases 1-20. 1.8 c.c. CCl <sub>4</sub> + .6 c.c. chenopodium . Magnesium sulphate after 2 hours.					Group 2. Cases 21-40. 1.8 c.c. CCl <sub>4</sub> + .6 c.c. chenopodium. Magnesium sulphate immediately.				
			First treatment: 1.8 c.c. CCl <sub>4</sub> , .6 c.c. chenopodium.			Test treatment: 3 c.c. chenopodium.		First treatment: 1.8 c.c. CCl <sub>4</sub> , .6 c.c. chenopodium.			Test treatment: 3 c.c. chenopodium.	
	Number.	Per cent.	Total 48 hours.	First 24 hours.	% for first 24 hrs.	Test count.	% of total.	Total 48 hours.	First 24 hours.	% for first 24 hrs.	Test count.	% of total.
All hookworms.....	21,219	100.0	10,267	8,860	86.3	351	3.3	10,211	5,831	57.1	390	3.7
Necators												
Total.....	19,357	91.2	9,327	8,249	88.6	126	1.3	9,547	5,459	57.2	157	1.6
Male.....	10,341	53.4	5,243	4,371	83.4	93	1.7	4,874	2,670	54.8	131	2.6
Female.....	9,016	46.6	4,284	3,878	90.5	33	0.8	4,673	2,789	59.7	26	0.6
Ancylostomes												
Total.....	1,862	8.8	740	611	82.6	225	23.3	664	372	56.0	233	26.0
Male.....	754	40.5	328	263	80.1	72	18.0	274	136	49.6	80	22.6
Female.....	1,108	59.5	412	348	84.5	153	27.1	390	236	60.5	153	28.2

TABLE V.

	<i>Necator.</i>								<i>Ancylostome.</i>								<i>Total.</i>			
	Female.				Male.				Female.				Male.							
	Trial	Test	Total	% Trial	Trial	Test	Total	% Trial	Trial	Test	Total	% Trial	Trial	Test	Total	% Trial	Trial	Test	Total	% Trial
Cases 1-20, Group 1.....	4,284	33	4,317	99.2	5,243	98	5,336	98.3	412	183	565	72.9	328	72	400	82.0	10,267	351	10,618	96.7
Cases 21-40 Group 2.....	4,673	26	4,699	99.4	4,874	131	5,005	97.4	390	153	543	71.8	274	80	354	77.4	10,211	390	10,601	96.3
Total.....	8,957	59	9,016	99.3	10,117	224	10,341	97.8	802	306	1,108	72.4	602	152	754	79.8	20,478	741	21,219	96.5



Only 8.8 per cent. of all hookworms recovered were ancylostomes and yet 61.8 per cent. of all worms removed by the test treatment of 3 c.c. of chenopodium were of this species.

TABLE VI.

	Necator.		Ancylostome.		Female.		Male.	
	Total.	% Trial.	Total.	% Trial.	Total.	% Trial.	Total.	% Trial.
Cases 1-20, Group 1. . . . .	9,653	98.7	965	76.7	4,882	96.2	5,736	97.1
Cases 21-40, Group 2. . . . .	9,704	98.4	897	74.0	5,242	96.6	5,359	96.1
Total. . . . .	19,357	98.5	1,862	75.4	10,124	96.4	11,095	96.6

Tables V and VI show that the combination is very effective against necator, removing 98.5 per cent. of this species, as compared with 75.4 per cent. of ancylostomes. 96.5 per cent. of all hookworms harbored were removed by the one treatment.

TABLE VII.

*Results of worm counts following treatment of hookworm disease with combination of three parts carbon tetrachloride and one part chenopodium, in adult dose of 2.4 c.c. (1.8 CCl<sub>4</sub> and .6 oil of chenopodium).*

	Group 1. Magnesium sulphate after 2 hours.	Group 2. Magnesium sulphate simultane- ously.	Total. Groups 1 and 2.
Cases treated. . . . .	20	20	40
Average number of hookworms per case. . . . .	531	530	530.5
Percentage of hookworms removed by trial treatment. . . . .	96.7	96.3	96.5
Percentage of cases cured (count). . . . .	10	10	10
Average worms harbored after trial treatment. . . . .	17.5	19.5	18.5
Number of cases with over ten worms. . . . .	12	11	23
Number of cases with over twenty worms. . . . .	7	8	15
Number of cases with over fifty worms. . . . .	1	1	2
Microscopic cures (Willis flotation). . . . .	7	7	14
Worm count cures. . . . .	2	2	4

It would appear that the combination is equally effective for male and female worms.

From Table VII it will be seen that the average worm count for the group is very high. Microscopic cures (Willis flotation) were found by test treatment to be false in ten out of fourteen cases. These ten cases had 229 worms of which 100 were females.

Although two of the four cases with no worms on test treatment harboured less than fifty worms, it was found by setting up a correlation table and plotting percentage removed by trial treatment, against total number removed by trial and test treatment, that there was an increased percentage removed by the trial treatment, as the number of worms harboured increased.

The large number of small and apparently immature hookworms that were expelled by the first treatment in heavily infested cases, and the relative absence of such forms in lightly infested cases and in stools from test treatments, indicates that heavily infested cases, as a rule, have a larger percentage of the less resistant forms than do lightly infested and previously treated cases.

#### CONCLUSIONS.

1. Hookworm infestation in Paraguay is very heavy. Fortunately, the infestation is over 90 per cent. of the less resistant and probably less harmful necator.

2. The combination of carbon tetrachloride, three parts, with oil of chenopodium, one part, in adult dose of 2.4 c.c. (1.8 c.c. of the former and .6 c.c. of the latter) is very effective in an area of low ancylostome infestation. No toxic symptoms were reported.\*

Like other anthelmintics, this combination gives a higher percentage of total worms removed in heavily infested cases than in those with few worms. This is probably due to a larger percentage of immature forms in heavily infested cases.

3. The simultaneous administration of magnesium sulphate tends to delay the expulsion of many worms until the second day. There appears to be, however, no diminution nor delay of anthelmintic action. A simultaneous reduction of toxicity and cost per person treated may be expected from the introduction of this method of administration in field work against hookworm disease.

\* It is only fair to state, however, that a fatal case of poisoning occurred in the field campaign, carried on simultaneously with this series, using the same combination—another confirmation of the incompatibility of carbon tetrachloride and alcohol.

## SUGGESTION FOR TREATMENT OF ASCARIS.

Only eleven ascarids have been recovered from cases to whom magnesium sulphate was administered simultaneously, all of which were expelled on the second day.

In areas where ascaris infestation is heavy, it may prove advantageous to give a purgative dose of magnesium sulphate, in saturated solution, simultaneously with the combined treatment to reduce absorption, and to follow this in three to five hours by a second dose of the magnesium sulphate in a twenty per cent. solution, to assure the early expulsion of dead worms.

*References.\**

1. HALL, MAURICE C.  
1921. Carbon tetrachloride for the removal of parasitic worms, especially hookworms. *Jour. Agric. Res.*, 21, 157-175.
2. SMILLIE, W. G., AND PESSOA, S. B.  
1922. Toxicity of carbon tetrachloride. *Bulletin of International Health Board*, 3, No. 2 (Supplement), October, 126-128.
3. LAMBERT, S. M.  
1924. Hookworm disease in Fiji. Report to Commanding Medical Officer. Fiji. February 14. Suva.
4. HALL, MAURICE C., AND SHILLINGER JACOB E.  
1924. The effect of magnesium sulphate simultaneously administered on the efficacy and safety of carbon tetrachloride for the removal of hookworm. *Am. Jour. Trop. Med.*, 4, No. 1, January.
5. Quoted from HALL AND SHILLINGER (4): MACET D. I. AND FINESILVER E. M.  
1922. The effect of saline purgatives on the absorption of other drugs. *Bull. Johns Hopkins Hospital*, 33, 330-338.
6. LAMBERT S. M.  
1923. Hookworm disease in Fiji. Report to Commanding Medical Officer. Fiji. Suva. 1-2.
7. LEACH, C. N., HAUGHWOUT, F. G., AND ASH, J. E.  
1923. The treatment of hookworm infestation with carbon tetrachloride. *Philippine Journal of Science*, 23, No. 5, November, 455-512.
8. DARLING, S. T., BARBER, M. A., HACKER, H. P.  
1915. Hookworm and malaria research in Malaya, Java and the Fiji Islands. Report of Uncinariasis Commission to the Orient. *International Health Board. Publication No. 9.*
9. DARLING, S. T., AND SMILLIE, W. G.  
1921. Studies on hookworm infection in Brazil. First paper. *Monographs of the Rockefeller Institute for Medical Research. No. 14, February 1.*

\* No attempt has been made to give a complete list of references. Only those are included here to which direct reference has been made in this article.